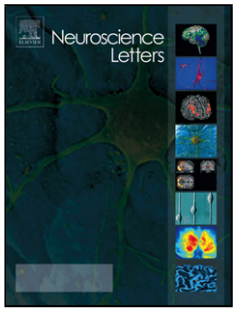
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COVID-19 and psychosis risk: real or delusional concern?

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COVID-19 and psychosis risk: real or delusional concern?

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Highlights

- Viruses and immune function have been associated with psychosis through genetic and epidemiological research.
- We critically evaluate the case for psychosis in COVID-19 through analysis of reported cases and historical precedents.
- Potential infectious, post-infectious and neurodevelopmental aetiologies are explored.
- Further appraisal of potential neurobiological and psychosocial mechanisms of 'COVID-19 psychosis' is urgently needed.

Abstract

Historical epidemiological perspectives from past pandemics and recent neurobiological evidence link infections and psychoses, leading to concerns that COVID-19 will present a significant risk for the development of psychosis. But are these concerns justified, or mere sensationalism? In this article we review the historical associations between viral infection and the immune system more broadly in the development of psychosis before critically evaluating the current evidence pertaining to SARS-CoV-2 and psychosis risk with regards to

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psychosis as an acute or post-infectious manifestation of COVID-19. We review the 42 cases of psychosis reported in infected patients to date. We discuss the potential implications of in utero infection on subsequent neurodevelopment and psychiatric risk. Finally, in the context of the wider neurological and psychiatric manifestations of COVID-19 and our current understanding of the aetiology of psychotic disorders, we evaluate possible neurobiological and psychosocial mechanisms as well as the numerous challenges in ascribing a causal pathogenic role to the infection.

Keywords: Psychosis, COVID-19, SARS-CoV-2, Neuropsychiatry, Neurology, Psychiatry, Schizophrenia, Encephalitis.

Introduction

Psychosis is a highly disruptive syndrome with many aetiologies characterised primarily by delusions, hallucinations, and disorganised thought, speech and behaviour (1). Since the start of the COVID-19 pandemic case reports and series of apparent COVID-19-associated psychosis have emerged. There is increasing urgency for a critical evaluation of the nature and strength of this association.

Since before the COVID-19 pandemic, the field of psychiatry had witnessed renewed interest in a classical hypothesis: that viruses can cause insanity, or more specifically psychotic disorders such as schizophrenia. This reappraisal occurred in the context of an 'inflammatory turn' within psychosis research in the 2010s (2), fuelled in part by genome-wide association studies converging on schizophrenia risk loci within the major histocompatibility complex (MHC) and in loci involved in B cell development (3); potentially including complement pathway loci (4) and by the recognition that brain-directed autoimmunity (e.g. to the N-methyl-D-Aspartate [NMDA] receptor) can cause psychosis as part of an autoimmune encephalitis syndrome, which in some cases may itself be 'post-infectious' in the sense of being triggered by a viral infection, usually of the CNS (5–7).

At the same time large-scale, well-controlled epidemiological data have emerged demonstrating clear associations between risk of developing psychotic disorders and previous a) hospitalisation or treatment for severe infection (8,9); b) number of severe infections (10); c) presence of autoimmune disease (11,12) and d) maternal infection during

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pregnancy (13). Moreover, relationships have been observed with the temporality of infection, such that risk of a new diagnosis of psychotic disorder is greatest soon after a diagnosis of infection (8,9). Furthermore, sero-epidemiological studies focussing on exposure to viruses, as indicated by pathogen-specific IgG responses, have implicated exposure to numerous viral and nonviral pathogens, including herpes simplex virus, Epstein-Barr virus, cytomegalovirus, influenza and *Toxoplasma gondii*, in psychosis risk (14,15), or risk of related phenomena including childhood psychotic experiences (16) or psychosis-associated cognitive dysfunction (17).

Literature suggesting an association between infection and psychosis can be traced many centuries (18,19), but even as far back as discussions of the 'psychoses of influenza' in the 17th and 18th century it was recognised that specific, predominantly respiratory infections, are temporally associated with acute psychosis (20). Most notably, hundreds of cases of acute post-influenzal psychosis were reported during and after the 1918-19 Spanish influenza pandemic. This was a phenomenon distinct from the near-contemporaneous epidemic of encephalitis lethargica, a syndrome of varied neuropsychiatric manifestations including psychosis, which may also have had a post-influenzal aetiology. The writings of Karl Menninger, whose case series and attempted ontologies of post-infectious neuropsychiatric presentations have taken on a keen relevance a hundred years later, are particularly clear: he describes cohorts of patients who presented with a schizophrenia-like psychosis weeks after influenza infection, taking great pains to distinguish these from patients who presented with psychotic symptoms as part of a more generalised impairment of consciousness or delirium (21–23). Menninger even describes one case who developed psychosis after the Spanish flu, having experienced his first episode after contracting influenza decades earlier during the 1889-92 Russian influenza pandemic. Following some of the 1918 patients for over 5 years, Menninger was stunned to see that many even with schizophrenia-like presentations made a full recovery, a trajectory that was at odds with the dominant Kraepelinian notion of dementia praecox, where patients with what we now term schizophrenia were predicted to experience progressive and irreversible neurocognitive decline (22). Similar acute psychoses have been described after subsequent influenza pandemics, and indeed in some cases following influenza vaccination (20). Infection with another pandemic virus, HIV, is now recognised as associated with an increased risk of both

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schizophrenia and acute psychosis (24). In contrast to this, it is important to note the relative dearth of psychoses reported during and after the 2009 H1N1 pandemic (25). Minimal cases were described in the literature, however, H1N1 surveillance studies focused primarily on neurological outcomes of infection, with examination of psychiatric sequalae less frequent (26,27).

In the 1980s and 1990s, following the demonstration that children born during the 1957 Asian influenza epidemic were at increased risk of developing psychosis (28), a large number of epidemiological and sero-epidemiological studies have attempted to elucidate the nature of the association between in utero viral exposure and the development of psychosis (29,30). Most mechanistic work on infection-related psychosis has taken place within this context: the maternal immune activation (MIA) model has reliably demonstrated that the offspring of pregnant mothers exposed to an inflammatory 'hit' are at greater risk of developing abnormalities across multiple anatomical, physiological and behavioural domains, many of which resemble observations in humans with psychotic disorders (31).

The foregoing suggests that COVID-19, a pandemic acute respiratory viral infection, may have the potential to cause psychosis, either acutely, or as a post-infectious manifestation, or as a neurodevelopmental pregnancy-associated risk factor. Interestingly a 2011 study found that exposure to two seasonal coronaviruses, HKU1 and NL63, was associated with increased risk of developing psychosis (32) – a study that has never been replicated (although the same group did describe an association between coronavirus seropositivity and a history of mood disorders (33)). In a recent systematic review and meta-analysis, Rogers et al. reported a rate of diagnoses of acute mania and/or psychosis in 0.7% of SARS and MERS patients, although most appear to have been attributed to the use of corticosteroids. Other studies that reported on individual psychotic symptoms including hallucinations and persecutory ideation reported rates between 2% and 5% in the acute phase and up to 4.4% in the post-acute phase of these infections, although given high levels of confusion in the acute phases of these critical illnesses it could be likely that such psychotic symptoms occurred as part of a more general delirium, where rates of psychotic symptoms are high (34,35).

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SARS-CoV-2 Infection

Despite rates of psychosis apparently increasing following historical pandemics, as yet there are relatively limited data correlating psychosis and SARS-CoV-2. Reports of primary psychotic disorders in infected individuals have emerged, but have been beset by both small sample size, and inadequate attention to potential confounding factors. In this section we will review the extant emerging literature associating COVID-19 with psychoses, highlighting case reports of phenomenological or mechanistic interest and larger case series (see Table 1).

Establishing a causal relationship between infection with a given pathogen and a putative manifestation requires a substantial evidential threshold, operationalised in the Bradford-Hill criteria (36). There are currently several specific complexities in assessing the true role of SARS-CoV-2 in neuropsychiatric disease, the most pertinent of which is separating the specific impact of the virus from both the broader disease response and the social, cultural and psychological circumstances in which an infection has occurred. That is, for this specific presentation at this specific time, is the virus directly pathogenic, or are we observing the sequelae of a pervasive inflammatory response in critically ill populations (37), or could the apparent association be masking more causally relevant, and well-established, causes of psychosis such as heightened stress, substance misuse or socio-economic hardship? Despite some reports of viral RNA in the CSF of patients with neurological manifestations (38,39), and clear evidence of *in vitro* and *in vivo* neuroinvasive potential (40) in the vast majority of patients there is no clear evidence of viral CNS access (41). Several reports have also been hindered by the neglect of potentially crucial iatrogenic influences on mental state; isolated wards and personal protective equipment (PPE) markedly limit 'normal' social interaction, and medicines such as corticosteroids, sedatives and anaesthetic agents can all have neuropsychiatric side effects; all of which have a potentially causative role in psychopathology. As this pandemic continues, the strength of evidence base will undoubtedly grow with it, and crucially longitudinal cohorts will begin to delineate the true impact, and potential underlying mechanisms, of SARS-CoV-2 on psychopathology.

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Acute Responses

Case reports

The first reported psychoses in this pandemic were described as caused, not by COVID-19, but as likely reactive responses to pandemic-related stress with psychotic content forming around the theme of infection. These included reports of a healthcare worker with an obsessional fear of infecting and subsequently killing themselves and their family (42), developing into derealisation, thought block and delusional thinking. Another example is a high functioning 38-year old woman, with no previous psychiatric history who developed an acute psychotic disorder stemming from her concern that she had caught the virus from her dentist due to their inadequate PPE (43). Her mental state eventually deteriorated to a perception that she was utterly controlled by the virus; she later unsuccessfully attempted to harm her family whilst following command hallucinations. In both instances, the psychoses quickly settled following treatment. Larger studies have reported on delusional content forming on topical issues in this pandemic; an Italian case series of six first episodes of psychoses, three patients reported the somatic delusion of being infected by the virus (44). Such content forming has also occurred postpartum, Chandra et al., report the case of a mother who suffered from persecutory auditory hallucinations which stated she had infected her baby with SARS-CoV-2, despite no infection (45). Although anecdotal, these cases highlight the integral role that stress can play in the development of psychiatric disorders. Numerous vulnerable individuals have now been placed in the most unprecedented social circumstances, with acute stressors from social isolation to real existential threat. Limited epidemiological evidence has hinted at a 25% increase in first episode psychosis (46) compared with last year, however this population-level study did not separate the causative factors behind first episode psychosis, from the formation of pandemic related delusions, to putative associations with viral infection.

Psychotic disorders have also been described in patients infected with SARS-CoV-2 (47,48) , although cautious scrutiny should ensue when examining these earliest cases and their claims of causality. Perhaps most crucially, care must be taken to assess whether a convincing case has been made that the 'psychosis' in question occurred as a syndrome in its own right and the presentation has not been erroneously labelled a psychosis but simply

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reflects one or two 'psychotic' symptoms (e.g. hallucinations and/or delusions) occurring as part of a more widespread alteration in mental state with an established physiological cause (e.g. delirium occurring in the context of hypoxia and/or sepsis) (49). This is not because COVID-19-associated delirium is not of clinical interest, but because psychotic symptoms are highly prevalent in delirium (34,35), which in turn is highly prevalent in critical illness generally including COVID-19 (50). The crucial questions centre on whether there are processes, biologically unique to SARS-CoV-2 that specifically predispose those infected to psychosis? As a broad principle, cases of new-onset psychosis reported either as occurring in the absence of severe respiratory illness or in cases without respiratory symptoms, or where delirium is explicitly clinically ruled out (i.e. no attentional impairment) with blood gas or electrolyte disturbances, sepsis, and iatrogenic causes excluded, may offer the most compelling grounds for the association between COVID-19 and psychosis as a syndrome in its own right.

Smith *et al.,* reported the first detailed case of psychosis in a patient with symptomatic SARS-CoV-2 infection who had no prior personal or familial history of neuropsychiatric disease. They reported a clinical course of insomnia and persecutory delusions which followed respiratory symptoms and COVID-19 diagnosis. Serum inflammatory markers were only mildly raised, and both neuroimaging (CT & MRI) and lumbar puncture (LP) were normal. Delirium screening was also negative. She improved over two weeks admission and remained symptom-free despite discontinuing risperidone in the community (51).

Case-series

A Spanish case series highlighted new-onset psychosis in several infected patients but did not explore the specific clinical details further (52), whilst an American case-series described three patients who developed psychoses during infection, albeit some had a prior psychiatric history (53). Cases have also been described in post-partum populations, with an Indian case series describing three infected mothers who developed brief psychotic episodes after giving birth. These patients were infected with SARS-CoV-2 but were asymptomatic. Two of the patients formed topical delusions concerning the virus, one believed that medical professionals were trying to infect her baby, whilst another was acutely paranoid that staff believed she was spreading COVID-19 (54).

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As the pandemic has grown, so too has the strength of evidence reported. Some of the clearest demonstrations have come from larger case series of neuropsychiatric manifestations, albeit retrospective in design. *Parra et al.,* reported on 16 patients with psychotic symptoms, and after excluding six for likely delirium, reported that ten patients had developed a first-onset psychosis approximately two weeks following somatic COVID-19 symptoms (55). None of the patients had any personal or familial psychiatric history or substance misuse. All patients presented with delusions, however in 60% there were also confusional/attentional symptoms. The authors state that they excluded patients that 'completely met the diagnostic criteria for delirium', however it is important to note that 50% of those described had recently been treated in ITU. They also describe that in those included, the delusions persisted longer than the confusional symptoms. Nonetheless, the temporal onset of the psychosis is interesting given epidemiological studies have shown a dose-dependent association between developing psychosis and proximity to infection (8), furthermore a similar interval has been observed in some schizophreniform presentations following H1N1 influenza infection (21). However, as with many other reports, it should be noted that several of the patients in this case series were taking therapeutics which could have confounded this association; for example seven of the patients were taking corticosteroids (55). Other large case series have reported high rates of first episode psychoses in otherwise asymptomatic patients with confirmed SARS-CoV-2 infection. *Iqbal et al.,* report nine cases of psychoses contemporaneous to diagnosis with COVID-19 (56). They screened for and ruled out concurrent delirium in these patients, and interestingly described that in those who presented with mania or psychosis half (9/18), had no prior psychiatric history.

The first report from the CoroNerve Study, a UK-wide surveillance study of hospitalised patients described that, of 125 patients with complete clinical details, 34 had altered mental status, with ten of those being a new-onset psychosis independently ratified by the attending neuropsychiatrist or psychiatrist (57). These were differentiated from other neuropsychiatric disorders in the cohort, such as six patients with neurocognitive (dementia-like) disorders, and four cases of new mood (affective) disorder. Interestingly, despite well documented rates of delirium in elderly patients with systemic infection

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overall, and with COVID-19 specifically, these new-onset psychoses were more frequently seen in younger members of the cohort; working-age adults.

Does the spectrum of COVID-19 associated neurology suggest mechanisms underlying reported associations with psychosis?

There is currently a lack of sufficient detail into the symptomatology of COVID-19 patients to be confident of either the true rates, or indeed the causes of acute psychiatric symptoms associated with infection. Whilst primary psychoses appear to be relatively rare, both encephalopathy and encephalitis have been reported more frequently in infected patients (50,57,58). Altered mental state has been reported in 5% of hospitalised patients (59), and is more prominent in critical care settings (50). In a prospective cohort study of 140 patients, Helms et al., reported delirium and/or abnormal neurological examination in 84% of patients (50). No consistent EEG and MRI hallmarks were discerned, but a varied range of abnormalities were present. Several underlying mechanisms have been postulated to cause these changes to mental state, including hypoxic brain injury, severe sepsis and a cytokine storm on a background of systemic hyperinflammation (60). Currently it is impossible to untangle whether these alterations in mental state represent encephalopathy from critical illness or encephalitis from direct neuroinvasion. Numerous reports of encephalitis have occurred in the literature on a background of concomitant COVID-19 (38,61,62), however very few of these reports have also been associated with viral RNA in CSF (38). PCR-negative CSF does not always preclude parenchymal neuronal infection, as it is increasingly recognised that intrathecal synthesis of anti-SARS-CoV2 antibodies is of utility in PCR negative cases (63). Furthermore, an absence of direct neuronal invasion by the virus does not preclude COVID-19 from causing neuropsychiatric syndromes via other mechanisms (36).

One of the most keenly debated – and potentially overemphasised – issues concerning the neuropsychiatry of COVID-19 is the virus' potential for neurotropism. The angiotensin-converting enzyme 2 (ACE2) receptor is one of several crucial viral entry points, however, the brain has relatively reduced endothelial expression of ACE2 compared to other organs (60). It is expressed however on oligodendrocytes and as evidence mounts it is becoming

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clearer that reduced receptor expression does not necessarily impede enhanced levels of infectivity in neural cells (64). CSF studies have established that viral RNA is rarely present in patients with COVID-19 (41), however, it has been isolated in several cases (39,65). Post-mortem studies have also demonstrated that viral invasion into neural tissue can occur (66), however it is very likely that these findings reflect viraemia in cerebral vasculature. Identification of true neuroinvasion would require more sensitive techniques, such as fluorescence in situ hybridisation.

Several *in vitro* studies have demonstrated the potential of SARS-CoV-2 for direct neuronal invasion (67,68), findings further replicated in murine brains (40). '*In silico'* methods of gene discovery have also driven hypothesises generation for protein-protein interaction networks of genes that may interact with SARS-CoV-2 (69), potentially implicating Integrin beta-1 as an ACE2 binding protein which is highly expressed in the brain. Preclinical modelling has proved difficult in SARS-CoV-2; murine models capturing sufficient disease severity to be externally valid are only just surfacing (Ki-ACE2 transgenic mouse model) (70), whilst *in vitro* models have not captured the systemic nature of COVID-19 (60). Importantly, as in many infection-associated neurological conditions, acute neurotropic invasion is not the only mechanism by which a virus can cause neuropsychiatric disease.

Several classically 'post-infectious' autoimmune disorders have been associated with SARS-CoV-2 infection, including Guillain-Barré Syndrome (GBS) (71) and acute disseminated encephalomyelitis (72). There has been increasing interest this decade into a group of autoimmune encephalitides thought to be caused by antineuronal antibodies, several of which have also been linked to psychosis, with the most common antibodies targeting the NMDA-R. Furthermore, such autoantibodies have been shown to cause a psychosis-like phenotype in both passive and active transfer animal models (73,74).

In May 2020 a patient with NMDA-R encephalitis and concomitant SARS-CoV-2 was described, presenting with psychomotor agitation, anxiety, thought disorganisation, persecutory delusions and auditory hallucinations before developing fever and difficulty breathing and deteriorating to profound confusion, dyskinesias and autonomic instability (75). He had a significant substance use background (cannabinoids, cocaine and

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phencyclidine) but no other psychiatric history. NMDA-R antibodies were seen on a second CSF sample and his condition was reported as improving with immunotherapy. Other groups have reported CSF NMDA-R antibodies in patients with COVID-19 and immunotherapy-responsive psychosis (76) and in new-onset refractory status epilepticus (77) as well as a more typical presentation of NMDA-R encephalitis (77). An intriguing case series described CSF autoantibodies in 11 patients with severe SARS-CoV-2 infection and a range of neurological symptoms (78) . Increased levels of neurofilament light, a marker of axonal damage, were noted in all of the seven specifically tested patients. A high frequency of serum autoantibodies was present across the cohort, including anti-Yo and NMDA-R. There is a possibility that these unidentified antibodies could be disease-causing and thus treatable. A case of catatonia in a previously healthy man with COVID-19 has also been reported (79). Although on initial CSF sampling there was no evidence of established antineuronal antibodies, the patient deteriorated displaying severe autonomic instability; he was treated with plasmapheresis for suspected autoimmune encephalitis. Immunohistochemistry detected IgG autoantibodies against several murine neuronal proteins in the patient's serum and initial CSF sample. Post-treatment CSF IgG immunoreactivity was notably reduced, possibly indicating a novel but treatable form of psychopathology stemming from autoimmune encephalitis in the context of SARS-CoV-2 infection. It is now well established that neuronal autoantibody-associated CNS syndromes can present with exclusively or predominantly psychiatric syndromes (80), and so the possibility exists of such an 'autoimmune psychosis' (5) occurring in a post-COVID context. Beyond conventional CNS autoantibodies which are tested in routine practice, further research is needed to evaluate whether SARS-CoV2 infection-related psychosis is associated with the development of novel autoantibodies directed against CNS antigens.

In some cases, the relevant mechanism remains unclear despite suggestive terminology. For example, 'acute parainfectious encephalopathy' with psychosis has been described in a 55-year-old female with no prior psychiatric history 2-weeks following diagnosis of COVID-19 and the onset of respiratory symptoms (58). She demonstrated odd ritualistic behaviour and delusional thinking, she also reported auditory hallucinations. Neuroimaging and CSF were normal, and the psychosis persisted well past an acute confusional states. After three weeks of treatment, including antipsychotics she settled.

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One potentially relevant mechanism involves the so-called 'cytokine storm' observed in some patients with severe COVID-19 (as well as, intriguingly, H1N1 influenza) - although notably pro-inflammatory cytokine increases occur in milder cases also (27). There is substantial meta-analytical evidence for elevation of pro-inflammatory cytokines in cases of primary psychotic disorders, and indeed drugs targeting specific cytokines can cause psychosis (81–84). In one case of psychosis following resolution of a relatively mild COVID-19 pneumonia in a 55-year-old woman, there was evidence of increased peripheral TNF-alpha, although IL-6, which has also been associated with psychosis risk, was normal (85). CSF cytokines were not measured, but this may represent an interesting future strategy in cases of psychosis putatively associated with COVID-19. These findings may come to be understood as reflective of innate vulnerability factors. Gene sequencing in 659 individuals with life-threating SARS-CoV-2 found enrichment for rare loss-of-function variants in the genes that control TLR3- and IRF7-dependent type I interferon immunity to influenza virus. The authors estimate that these vulnerabilities were seen in 3.5% of the most severely affected patients, however, this likely reflects impairments in control of viral replication as opposed to immunopathogenic processes effecting the CNS.

Neurodevelopmental implications of in utero exposure

One area of psychosis research which may offer a precedent for the longitudinal impact of COVID-19 is the association between in utero events and offspring neurodevelopment. Schizophrenia is rooted in neurodevelopmental origins (86), with the disorder sharing broad genetic underpinnings with classical neurodevelopmental disorders such as autism spectrum disorder and developmental delay (87); it also develops more commonly in offspring born to mothers who have experienced stressors in utero. Reported stressors which have been associated with enriched offspring rates of the disorder include recent bereavement or family illness (88), and maternal infection (89).

Several cross-sectional studies have reported on obstetric cohorts of expectant mothers, both with (90) and without (91) concurrent SARS-CoV-2 infection. These have demonstrated marked changes in maternal stress, health anxiety and socio-behavioural interactions (91,92). In one cohort, levels of anxiety and depression were significantly higher when

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compared to a pre-pandemic group, and although extrapolation cannot be made as to the foetal impact, there is significant precedent for this to cause concern for offspring neurodevelopment (88). It should be noted that some studies have reported no significant differences in median measures for anxiety and depression (GAD-9, PHQ-9) respectively in groups of mothers with and without SARS-CoV-2, however, they did show in both groups that anxiety did rise, following the pattern of the rise in infections more broadly (90). These maternal anxieties were multifaceted, concerns of contracting the virus, as well as not having adequate care or support during the pregnancy itself. Many countries are still employing strict social distancing in all healthcare settings, meaning that mothers can only attend appointments and scans in isolation. Mothers have reported significant anxiety related to the infection causing pre-term births and structural abnormalities in their children (92), fears that will be heightened by facing such appointments alone.

Without longitudinal studies, it will be difficult to appreciate the health outcomes of offspring born during this pandemic, to mothers both with and without infection. Even for viruses like influenza, the strongest implicated maternal infection for schizophrenia (20), there is only limited evidence of direct placental transfer of the virus pathogens (93). Thus, the effects seen in these epidemiological studies has been proposed to be a result of maternal immune activation, (94) a group of processes which have also been linked with other neurodevelopmental disorders like ASD. Recent advances in animal models have also been able to link these hypotheses to neurocognitive deficits in murine offspring of infected mice, such deficits that could be matched to characterised endophenotypes of common psychiatric disorders (94). This has been conceptually visualised as an ‘inflammatory hit’, which along with genetic predisposition and psychosocial factors could increase one’s risk of developing psychosis. Maternal immune activation has been suggested to lead to psychosis through multiple potential trajectories, by directly impairing neurodevelopment or by impaired neurodevelopment leading to a behavioural phenotype which could predispose the offspring to environmental risks for psychosis.

The case for causality and future directions.

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The SARS-CoV-2 pandemic is resulting in a rapidly evolving clinical picture. Nevertheless, already it is clear that infected patients can exhibit a range of neuropsychiatric symptoms. However, underlying pathological mechanisms have not been established, and much of the literature remains conceptual and extrapolated from small studies in this pandemic and studies of previous epidemic viral infections. It is clear from this review of the available evidence that the COVID-19/psychosis association does not meet the Bradford-Hill criteria of *strength, consistency, specificity,* or *temporality* required for a confident determination of causality. While there is scant evidence as yet for a *biological gradient* relating intensity of infection or viral load to psychosis severity, we have seen that there is *biological plausibility* to the association. Nonetheless, it is an accepted principle that establishing causality with regards to putatively rare outcomes is more challenging, and it is likely that the relevant literature will continue to grow exponentially; furthermore, analogy with previous pandemics, and the possibility of experimental studies assessing the impact of SARS-CoV-2 infection on brain and behaviour, mandate ongoing research interest and funding.

Several considerations are necessary when scrutinising any case for neuropsychiatric sequalae in infected patients, especially psychosis. Firstly, the importance of iatrogenic factors cannot be understated, both medical and psychosocial. For the former, the neuropsychiatric side effects of therapies such as corticosteroids and quinolones should be gauged, and for the latter, the psychosocial stressors provoked by the pandemic more broadly, and the isolation faced by both the public and isolated patients confronted by unfamiliar medical staff in PPE. Secondly, the majority of patients with COVID-19 will have a mild illness and exhibit no neuropsychiatric manifestations; the literature has a clear selection bias for critically ill and hospitalised patients towards the most severe end of the clinical spectrum; in these cases care must be taken to exclude the possibility that psychotic symptoms are occurring as part of a delirium. A final consideration that has not been systematically assessed to date concerns the scale of a pandemic and the numbers of individuals infected. If psychosis (or indeed any other putative neuropsychiatric sequela) appears to occur more frequently in infected patients during a pandemic, could this simply be because it is a rare complication of almost any respiratory viral infection, the incidence of which has been driven up dramatically by the total number of infections? This could well be an important distinction between the rates of psychosis associated with both Spanish Flu

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and the 2009 H1N1 pandemics. Establishing the 'true' incidence rate of psychosis in COVID-19 as compared to other infections is however far from trivial, not least because of unprecedented levels of population testing, along with many of the confounders outlined above.

Conclusion

Evidence from historical pandemics strongly suggests that infection, particularly with viral respiratory pathogens, is a risk factor for schizophrenia-like illnesses in infected patients. What may not become apparent for many years, however, is the role that in utero infection will play in the neurodevelopment of offspring born during this pandemic, both to mothers with and without the virus. While only time will unpick which pathogenic mechanisms are driving neuropsychiatric associations, it is likely to be one or many of the following: 1) direct neuronal viral infection, 2) post-infectious neuronal autoimmunity, 3) vasculopathies from impaired coagulation and 4) systemic (e.g. inflammatory) effects of a pervasive severe pathogen and/or critical illness. Unlike in 1918-19, psychiatric neuroscience and epidemiology are now equipped with the tools to answer questions that have haunted the discipline of psychiatry for over a decade (21,22). A combination of longitudinal studies of infected individuals and sero-epidemiological studies (e.g. measurement of antibody titres) in new-onset psychoses, alongside mechanistic and animal studies employing psychosis-relevant paradigms, may help elucidate causation. Against the background of the tragedy of the COVID-19 pandemic, there may yet emerge the opportunity for greater understanding of a disabling mental illness.

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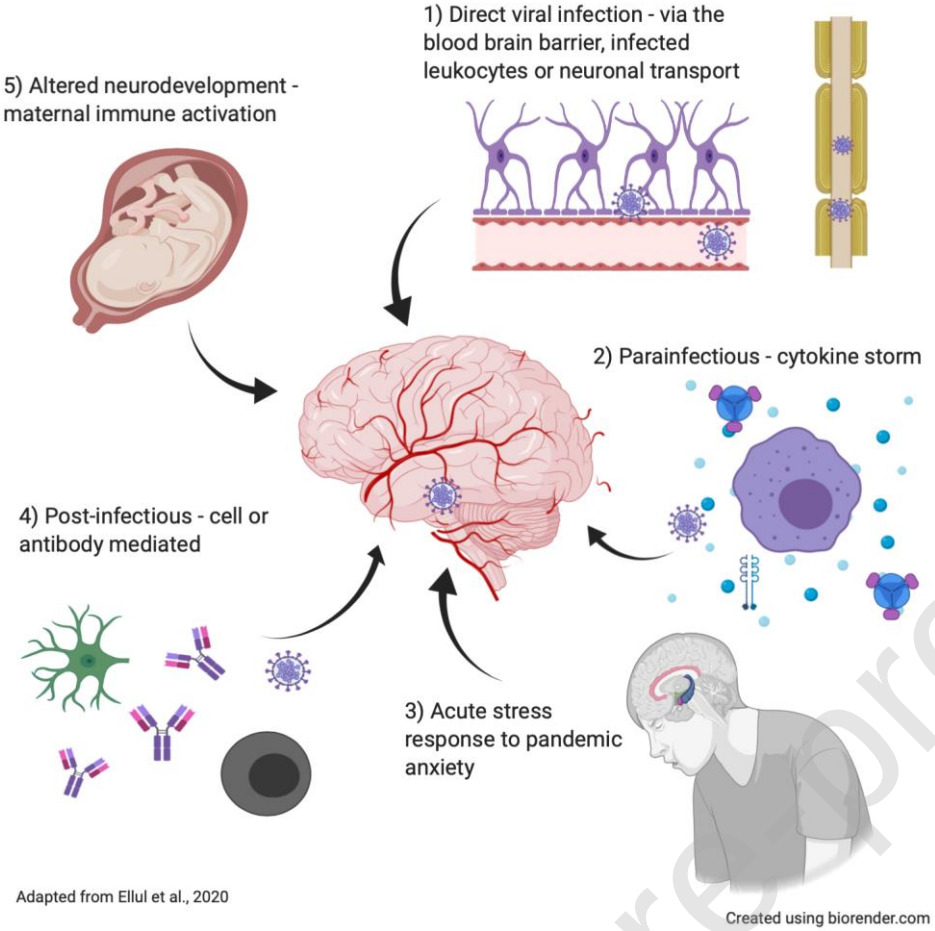


Figure 1: Potential mechanisms of COVID-19 psychosis based on knowledge of other viruses, adapted from Ellul et al., 2020 (98) **created with BioRender.com.**

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Table 1: Reported cases of psychosis or psychotic symptoms in patients with SARS-CoV-2 infection, and those with pandemic-related stress.

Study	Design	SARS-CoV-2 infection	Specific population	Cases of psychosis (n)	Mean age	Male/Female	Details of psychosis	Past psychiatric history	Other info
Oca Rivas et al (42)	case-report	n	Healthcare professional	1	60	1/0	Obsessional delusions about infecting family	nil	
Huarcaya-Victoria et al (43)	case-report	n	-	1	38	0/1	Persecutory and command hallucinations to harm family	nil	
Zulkifli et al (95)	case-report	n	-	1	31	1/0	Extreme stress related to COVID-19 pandemic	nil	
D'Agostino (44)	case-series	n	-	6	53.3	3/3	3 had somatic delusion of infection	nil	
Moideen et al (76)	case-report	n	Anti-NMDA-R Abs (CSF)	1	17	1/0	2-weeks history of fever, urinary incontinence, slurred and incoherent speech, overactivity, mood incongruent and reduced sleep. Psychosis improved with immunotherapy.	nil	New-onset psychosis with anti-NMDA-R Abs. Also reported significant stress related to COVID-19 pandemic
Panariello et al (75)	case-report	y	Anti-NMDA-R Abs (CSF)	1		1/0	Thought disorganization, persecutory delusions and auditory hallucinations	substance use background (cannabinoids, cocaine and phencyclidine)	Clinically improving with immunotherapy
Correa-Palacio et al (96)	case-report	y	-	1	43	1/0	Developed psychosis around 2 weeks after COVID-19 somatic symptoms, had also been treated with corticosteroids	nil	History of cocaine misuse
Noone et al (47)	case-report	y	-	2	41.5	1/1	Severe psychosis and mania	nil	
Rentero et al (52)	case-series	y	-	Not reported	-	-	Psychotic symptoms characterised by thoughts of reference and structured delusional. To note patients with comorbid acute delirium remained psychotic once delirium resolved.	nil	
Ferrando et al (53)	case-series	y	-	3	32.3	2/1	All had new and recent-onset severe anxiety, agitation, paranoia, disorganized	n=2 had pre-existing psychiatric illness	Other confounders present: homelessness and substance abuse

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							thinking. None had somatic symptoms of COVID-19.		
Smith et al (51)	case-report	y	Healthcare professional	1	36	0/1	insomnia and persecutory delusions which followed respiratory symptoms	nil	
Parra et al (55)	case-series	y	-	10	54.1	6/4	All patients presented with delusions (50% of were highly structured), orientation/attention disturbances (60%), auditory and visual hallucinations (40% and 10%, respectively).	nil	In 80% psychosis appeared >2 weeks after the first somatic manifestation of COVID-19 and resolved <2 weeks.
Varatharaj et al (57)	case-series	y	-	10	-			new onset psych disorders, unclear whether any history?	Differentiated from neurocognitive (dementia-like) disorders new mood (affective) disorder. More common in younger patients.
Iqbal et al (56)	case-series	y	-	9	-			Half of those with psychosis or mania had no past psychiatric history: no concurrent delirium diagnoses. HOW MANY WERE ASYMPTOMATIC FROM RESP POV?	
Subramanyam et al (54)	case-series	y	Postpartum	3	23.3	0/3	3-7 days duration, in 2 patients, psychotic symptoms concerned COVID-19	nil	
Chandra et al (45)	case-series	n	One patient postpartum	2	29	0/2	one patient believed the family deity had cursed her with COVID-19, whereas the other patient was obsessional about her or her baby contracting SARS-CoV-2.	nil	
Lu et al (97)	case-report	Y	-	1	51	1/0	Manic episode, with grandiose delusions, early morning waking and excitable yet irritable. At all times was alert.	nil	SARS-CoV-2 IgG positive, but PCR negative, in CSF.
Lim et al (85)	case-report	y	-	1	55	0/1	Initial delirium followed by persistent florid psychosis: persecutory delusion, complex hallucinations and Capgras phenomenon, lasted 40 days.	nil	Elevated serum tumour necrosis factor (TNF)-α.

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